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ORIGINAL COMMUNICATION

A multimodal approach to understanding motor impairment and disability after stroke

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Abstract Many different measures have been found to be related to behavioral outcome after stroke. Preclinical studies emphasize the importance of brain injury and neural function. However, the measures most important to human outcomes remain uncertain, in part because studies often examine one measure at a time or enroll only mildly impaired patients. The current study addressed this by performing multimodal evaluation in a heterogeneous population. Patients ($n = 36$) with stable arm paresis 3–6 months post-stroke were assessed across 6 categories of measures related to stroke outcome: demographics/medical history, cognitive/mood status, genetics, neurophysiology, brain injury, and cortical function. Multivariate modeling identified measures independently related to an impairment-based outcome (arm Fugl-Meyer motor score). Analyses were repeated (1) identifying measures related to disability (modified Rankin Scale score), describing independence in daily functions and (2) using only patients with mild deficits. Across patients, greater impairment was related to measures of injury (reduced corticospinal tract integrity) and neurophysiology (absence of motor evoked potential). In contrast, (1) greater disability was related to greater injury and poorer cognitive status (MMSE score) and (2) among patients with mild deficits, greater impairment was related to cortical function (greater contralesional motor/premotor cortex activation). Impairment after stroke is most related to injury and neurophysiology, consistent with preclinical studies. These relationships vary according to the patient subgroup or the behavioral endpoint studied. One potential implication of these results is that choice of biomarker or stratifying variable in a clinical stroke study might vary according to patient characteristics.

Keywords Neuroimaging · Impairment · Disability · Stratification · Biomarker · Motor system

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Introduction

Behavioral outcomes after stroke show substantial variation across patients. Many factors contribute to this, including differences between patients prior to stroke, in the stroke injury itself and in post-stroke brain plasticity. Inter-subject variability in patients with stroke complicates efforts to evaluate new therapies, including efforts to stratify patients in clinical trials [1] or to develop reliable biomarkers [2].

Numerous measures have been found to correlate with outcome after stroke in humans. Examples include age [3], comorbidities such as diabetes [4], cognitive status [5], depression [6], and genetic variation [7] as well as neuroimaging measures such as infarct volume [8], corticospinal tract (CST) integrity [9], and cortical function [10]. However, the measures most critical to outcomes in patients with stroke remain uncertain, in part because few studies have examined multiple variables in parallel. A multimodal approach could help identify the factors most closely linked with behavioral outcome after stroke.

The current study adopted such a multimodal approach, with a focus on the motor system. In a cohort of patients who

reached a plateau in behavioral recovery after stroke, variables in 6 categories were measured: demographics/history, cognitive/mood, genetic, neurophysiology, brain injury, and cortical function. The primary study hypothesis, based on the preclinical literature [11–13], was that measures of brain injury and neural function would have the strongest relationships with final level of motor impairment after stroke.

Two secondary hypotheses were also examined. The first was that the correlates of motor outcome after stroke vary in relation to severity of the deficits. The heterogeneity of stroke in humans suggests that differences may exist in the biology of recovery across patient subgroups. A better understanding of biological differences in stroke subgroups might inform (1) stratification approaches in clinical trials of restorative therapies after stroke and (2) the extent to which published reports generalize, given that many prior studies have focused on patients with mild deficits [14]. The second hypothesis was that the correlates of motor outcome after stroke vary across dimensions of the World Health Organization International Classification of Functioning, Disability, and Health (WHO ICF) [15]. Specifically, correlates of impairment (loss of body functions and structures) are hypothesized to differ from correlates of disability (activities limitations). Less is known about the neurobiological basis of post-stroke disability, as compared to impairment, although such information is important given that measures of disability are directly linked with patient functional status [16] and that such measures have only a limited relationship with level of impairment.

Materials and methods

Patients

Forty-one patients with stable motor deficits early after stroke were recruited. Inclusion and exclusion criteria appear in Table 1. Of the 41 enrollees, 4 could not complete MRI due to claustrophobia/anxiety and 1 was found ineligible after baseline assessments, leaving 36 patients (Table 2). All patients provided informed consent. The study was approved by the UC Irvine Institutional Review Board.

Demographics/history

Medical history was obtained, and hospitalization records were reviewed.

Cognitive/mood status

A single rater performed all behavioral assessments, which included Mini-Mental State Exam (MMSE) and Geriatric Depression Scale [17].

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years	Contraindication to MRI
Diagnosis of stroke 11–26 weeks prior	Severe cognitive impairment
Residual arm motor deficit (ARAT <52 or 9-hole peg test score >25 % longer than with unaffected hand)	Concurrent diagnosis affecting arm/hand function
Preserved voluntary movements in distal upper extremity (≥5° range of motion in affected index metacarpophalangeal joint or wrist)	Arm motor status not at stable plateau

Table 2 Patient characteristics

Age (years)	58.4 ± 13.8 (21–86)
Gender	10 F/26 M
Time post-stroke (months)	4.4 ± 1.1 (2.5–6.0)
Handedness	2 L/34 R
Diabetes mellitus	10 Y/26 N
Hypertension	18 Y/18 N
Hypercholesterolemia	16 Y/20 N
Fugl-Meyer arm motor score	35.0 ± 14.5 (14–60)
Mini-Mental State Exam	28 [25–30]
Geriatric Depression Scale	2.5 [1.25–4.75]
BDNF val^{66}met polymorphism present	11 Y/25 N
ApoE4 allele present	8 Y/28 N
Side of stroke	19 L/17 R
Infarct volume (cc)	31.7 ± 48.6 (0.5–178)

For the 36 individuals with stroke, values presented are mean ± SD (range) or median [IQR]. For the FM scale, normal score is 66; for MMSE, 30; for both, higher score is better. For the Geriatric Depression Scale, normal score is 0 and lower score is better

At this exam, impairment was measured using the arm motor Fugl-Meyer (FM) scale [18], and disability, using the modified Rankin Scale (mRS) [19]. Stable arm motor status was operationally defined by obtaining a second baseline FM score 7–21 days after the first; stability was present if the second FM score was within 3 points of the first. Handedness was determined using the Edinburgh Handedness Inventory [20].

Genetics

A blood sample was obtained, and presence of the brain-derived neurotrophic factor (BDNF) val^{66}met polymorphism and the ApoE4 allele was each determined, as described previously [7].

Neurophysiology

Patients underwent transcranial magnetic stimulation (TMS) of ipsilesional motor cortex. Motor evoked potential

(MEP) amplitudes were measured in the paretic first dorsal interosseous muscle at rest [21]. In sum, the site of lowest motor threshold (LMT) in the ipsilesional hemisphere that elicited a suprathreshold response of 0.5 μV [22] in the stroke-affected first dorsal interosseus (FDI) muscle at rest was identified. If an LMT was found, TMS was applied at four stimulus intensities (90, 110, 130, and 150 %). If an MEP was detectable, reflecting neurophysiological integrity, latency to MEP was calculated (measured in ms, determined at 110 % of resting motor threshold and reflecting speed of motor system conduction), as well as the input/output recruitment curve (which finds the slope of the plot looking at MEP in relation to the 4 TMS stimulation levels and reflects recruitment and reserve of stimulation targets [22, 23]). Presence of a TMS-elicited MEP was also categorized as present or absent. If no MEP greater than 0.5 μV was elicited in and around motor cortex after four stimulations at the maximum output of the TMS coil, then MEP was defined as absent. For maximal safety, subjects did not undergo TMS if contraindicated, e.g., due to calvarial defect or usage of certain medications [21, 24]. Due to these criteria, 16 subjects did not undergo TMS.

Brain injury

Image acquisition: MRI images were acquired using a 3.0T Philips Achieva system. Imaging included both anatomical (high-resolution T1-weighted images, T2-FLAIR, and diffusion tensor imaging (DTI)) and functional MRI (fMRI). For the T1-weighted image, parameters included repetition time (TR) = 8.5 ms, echo time (TE) = 3.9 ms, slices = 150, and voxel size = 1 × 1 × 1 mm^3. For the T2-FLAIR image, parameters included TR = 11,000 ms, TE = 125 ms, slices = 31 slices, and voxel size = 0.58 × 0.58 × 5 mm^3. One set of diffusion-weighted images was acquired using 32 directions, *b*-value 1,000 smm^{-2}, 60 slices, and voxel size = 1.75 × 1.75 × 2 mm^3.

Image analysis: Image analysis was performed blinded to clinical data. In sum, three classes of brain injury metrics were extracted: (1) total brain injury (infarct volume); (2) gray matter injury (to primary motor cortex (M1), to dorsal premotor cortex (PMd), and total cortical injury); and (3) white matter injury (overlap with corticospinal tract (CST) and per DTI fractional anisotropy (FA) values within ipsilesional cerebral peduncle).

Infarct volume: Using the MRI image analysis program MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), each subject's infarct was outlined by hand on the T1-weighted MRI image, as informed by the T2-FLAIR image. All areas of injured tissue (i.e., the infarct core and surrounding diffuse white matter injury) were included. When multiple spatially separate foci of injury were present, they were all summed into a single-stroke mask. The resulting stroke masks were binarized and then spatially transformed into MNI standard stereotaxic space using FSL. We have found good intra-rater reliability (Pearson's $r = 0.998$, $p < 0.0001$; intraclass correlation coefficient = 0.998) and inter-rater reliability ($r = 0.994$, $p < 0.0001$; intraclass correlation coefficient = 0.98) with this method, in a separate analysis of 10 subjects who were 3–6 months post-stroke.

Gray matter injury: To determine the contribution of gray matter motor system injury to behavioral gains, each patient's baseline T1-weighted image was inspected to evaluate stroke-related injury to cortex of M1 (i.e., precentral gyrus), cortex of PMd, and the entire cerebral cortex. The regions of interest (ROI) for M1 and for PMd were drawn on the 1 × 1 × 1 mm MNI T1 template in FSL. The M1 ROI consisted of the posterior bank of the precentral gyrus, whereas the PMd ROI consisted of the posterior bank of the middle frontal gyrus anterior to the precentral sulcus. The cerebral cortex ROI was generated by segmenting the same MNI template using the FAST module and isolating the segmented deep gray matter. Each patient's stroke mask was transformed into MNI space using the same template. Those two images were then multiplied to generate an overlap image. The number of voxels of the infarct that overlapped with the ROIs was counted. Injury was measured both as a continuous variable (i.e., the number of damaged voxels within the ROI) and as a dichotomous variable (the ROI was injured or not).

Corticospinal tract injury: Using the diffusion-weighted images, white matter integrity within the CST was quantified as mean FA [25] within a peduncular ROI, using FSL (www.fmrib.ox.ac.uk/fsl). Diffusion data were corrected for eddy currents and head motion using a 3D affine registration. Fractional anisotropy maps were then generated by fitting a diffusion tensor model at each voxel (DTIFIT module in FSL). An ROI was then drawn on the axial slice that showed the greatest cross-sectional area of the cerebral peduncle (CP) [26, 27]. The colorized FA image [28] was used to guide ROI drawing, ensuring ROIs did not extend into the substantia nigra. The region of the CP was selected for this measure because of its large content of descending motor fibers and because it was located remotely from all but one of the subjects' stroke lesions.

A second method was used to measure corticospinal tract injury: the amount of overlap in MNI stereotaxic space between each subject's infarct and the normal M1 corticospinal tract [29–31]. The normal tract was generated using diffusion tensor tractography in 17 healthy controls as described previously [29]. In sum, in these 17 subjects, after DTI images were corrected for eddy current distortions and head motion artifacts, FSL's BEDPOSTX program was used to generate probability distributions of

diffusion parameters at each voxel, including modeling for diffusion of crossing fibers along two directions. Seed regions for tractography were placed in the precentral gyrus, and a second seed ROI was placed in the cerebral peduncles. Tractography was initiated from a mask of the precentral gyrus using the CP as a waypoint mask. The resulting tracts were transformed into MNI space, binarized, and summed to create a group corticospinal tract. This tract was then thresholded to include only voxels in which at least 6 of the subjects were included. To simulate damage to groups of axons, the CST was divided into 16 separate longitudinal subsections. The binary stroke mask was overlapped onto each CST subsection. For each subject with stroke, a CST subsection was classified as injured if more than 5 % of that subsection overlapped with the binary stroke mask. The percentage of CST injury was calculated from the summed number of damaged subsections divided by the total number of subsections, which was then converted to a percentage.

Cortical function

Image acquisition: Three runs of blood oxygenation level-dependent (BOLD) images were acquired for functional MRI (fMRI) using the following parameters: TR = 2,000 ms, TE = 30 ms, 31 slices with thickness 4 mm, and 1-mm interslice gap. Each of the three fMRI runs was 96 s (48 brain volumes), during which subjects viewed a video that guided the paretic hand to alternate between 24 s of grasp-release movements and 24 s of rest. An investigator observed movements during scanning to ensure compliance. Three measures of brain function were extracted from fMRI images: (1) activation beta (contrast) estimate; (2) activation volume, each measured in right and in left M1 and PMd; and (3) activation laterality index (LI) for M1 and PMd.

Functional data from the three BOLD fMRI runs were preprocessed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Preprocessing steps included realignment to the first image, coregistration to the mean EPI image, normalization to the standard MNI EPI template, and spatial smoothing (FWHM = 8 mm). Data were visually inspected for head movement after the realignment step. Data were rejected for subjects with >2 mm head displacement, and as a result, fMRI data for 7 subjects were excluded.

For statistical analysis, the fMRI data were modeled as a boxcar convolved with a hemodynamic response. A high-pass filter of 128 s was used to remove low signal changes. Functional run data were inspected for outliers due to excessive head motion (>1 mm translation or >0.2 radians rotation between each volume) and signal noise ($Z > 3$ from the mean image intensity) using the Artifact Detection Tool toolbox (http://www.nitrc.org/projects/artifact_detect). Any outliers were deweighted during statistical analysis. Single-subject *t*-maps (task versus rest) were generated using $p < 0.001$ uncorrected. Using the Marsbar toolbox [32], right and left ROIs were created within M1 and PMd, as well as a midline supplementary motor area (SMA) ROI, based on coordinates reported in a meta-analysis by Mayka et al. [33]). Peak beta contrast estimates and activation volumes were extracted in SPM8 using small volume correction. If no suprathreshold clusters were detected at $p < 0.001$ uncorrected, small volume correction was evaluated at $p < 0.01$. Percent signal change within the ROIs was also calculated in Marsbar.

Statistical analysis

Statistical analyses were conducted using JMP software (version 8.0.2, SAS Institute, Inc., Cary, NC).

Correlates of impairment (loss of body functions and structures): The above metrics were examined as independent variables in relation to an impairment-based dependent measure, arm motor FM score. First, bivariate screening examined the relationship that each independent variable had with the FM score, using two-tailed alpha = 0.05. When possible, parametric methods were used, with non-normally distributed variables transformed to a normal distribution, else nonparametric methods were used. Second, multivariate modeling was used. For each of the 6 categories of measurement, if at least 1 independent variable showed a significant bivariate relationship, the variable with the strongest correlation in that category was advanced into a stepwise forward multivariate model (using $p = 0.1$ to enter, $p = 0.15$ to leave).

Correlates of impairment among patients with mild deficits: Analyses were repeated examining only those patients in the top quartile of FM scores (FM > 47).

Correlates of disability (activities limitations): Analyses were repeated using a disability-based dependent measure, mRS score, which was dichotomized as none–slight disability (mRS score = 0–2) or moderate–severe disability (mRS score >2).

Results

Patients

Motor impairment was on average moderate–severe (FM = 35.0 ± 14.5, mean ± SD), with values spanning a wide range (FM scores 14–60). A wide range of disability was also present (mRS scores 1–4), with scores being 0–2 in 69 % of patients and >2 in 31 % of patients. One patient was excluded from DTI analysis because the stroke directly injured the region of interest within the cerebral peduncle,

7 patients were excluded from fMRI analyses due to excessive task-related head motion during scanning, and a contraindication to TMS (generally medication-related) was present in 16 patients, excluding neurophysiology analyses.

Demographics/history: Features for the 36 patients are presented in Table 2.

Cognitive/mood status: Overall, patients were not cognitively impaired or depressed (Table 2).

Genetics: Genotype frequencies were in Hardy–Weinberg equilibrium. The BDNF val^{66}met polymorphism and ApoE4 allele were present in 31 and 22 % of patients, respectively.

Neurophysiology: The 20 patients able to undergo TMS did not significantly differ from the 16 patients who could not in terms of age, FM score, or time post-stroke. An MEP could be elicited in only 5 of the 20 patients, and so TMS findings are presented dichotomously (MEP present/absent), as insufficient data were available to analyze the continuous TMS measure MEP amplitude.

Brain injury: Infarct volumes were moderate on average (31.7 ± 48.6 cc) and spanned a wide range (0.5–178 cc). The infarcts involved M1 in 42 %, PMd in 33 %, and any cortical gray matter in 72 % of patients (among whom volume of cortical injury averaged 26.8 ± 37.2 cc). Extensive CST injury was present by both methods. First, lesion–CST overlap was 51.6 ± 32 %, indicating substantial CST injury, with the full range of values (0–100 %) present. Second, DTI-derived values for mean FA within ipsilesional cerebral peduncle were lower compared to contralesional peduncle (0.37 ± 0.12 vs. 0.56 ± 0.10, $p < 0.0001$), indicating reduced ipsilesional CST integrity.

Cortical function: Paretic hand movement was generally associated with bilateral motor system activation. Ipsilesionally, significant activation was present within M1 in 93 % and within PMd in 90 % of patients; contralesionally, M1 activation was present in 90 %, and PMd in 100 % of patients. Functional activation in ipsilesional M1 was larger than in contralesional M1 ($p < 0.004$) or ipsilesional PMd ($p < 0.002$), whether examining beta estimates or activation volumes. Overall, activation was lateralized toward the ipsilesional hemisphere for M1 (LI = 0.41 ± 0.85) and contralesional hemisphere for PMd (LI = −0.19 ± 0.87).

Correlates of impairment

In 4 of the 6 assessment categories (demographics/medical history, cognitive/mood, neurophysiology, and brain injury), bivariate screening found a single independent variable to be significantly associated with FM score (Table 3): greater impairment (lower FM score) was associated with presence of hypertension, poorer cognitive

Table 3 Bivariate correlations of variables with motor impairment and disability

Assessment	Correlation with greater impairment (lower FM score)		Correlation with greater disability (higher mRS score)	
	r	*p*	*r*	*p*
Demographics/medical history				
Age	0.005	0.98	0.08	0.59
Time post-stroke	0.25	0.14	0.21	0.16
Gender	0.08	0.66		0.13
Diabetes mellitus (Y/N)	0.15	0.41		0.04[a]
Hypertension (Y/N)	−0.49	0.0032[b]		0.15
Hypercholesterolemia (Y/N)	−0.16	0.34		0.72
Cognitive/mood				
Mini-Mental State Exam	−0.34	0.048[a]	−0.38	0.01[a]
Geriatric Depression Scale	0.11	0.51	0.04	0.81
Genetic				
BDNF val^{66}met polymorphism present (Y/N)	−0.08	0.57		1.00
ApoE4 allele present (Y/N)	−0.09	0.55		0.68
Neurophysiology ($n = 20$)				
Presence of motor evoked potential (Y/N)	−0.74	0.003[b]		1.00
Brain injury				
Infarct volume (cc)	0.27	0.12	0.41	0.007[b]
M1 injury (Y/N)	0.26	0.14		0.03[a]
M1 injury (cc)	0.30	0.08	0.16	0.29
PMd injury (Y/N)	0.19	0.25		0.12
PMd injury (cc)	0.18	0.30	0.09	0.54
Total cortical injury (cc)	0.26	0.12	0.40	0.009[b]
Corticospinal tract integrity (ipsilesional FA)	−0.60	0.0001[c]	−0.52	0.0005[c]
Percent injury to CST (lesion overlap with CST)	0.27	0.11	0.24	0.10
Cortical function ($n = 29$)				
Ipsilesional M1 activation: beta estimate	−0.01	0.94	−0.12	0.46
Ipsilesional PMd activation: beta estimate	−0.03	0.87	−0.10	0.54
Contralesional M1 activation: beta estimate	0.30	0.12	0.10	0.57
Contralesional PMd activation: beta estimate	0.04	0.82	0.26	0.12
Ipsilesional M1 activation volume	−0.10	0.60	−0.21	0.20
Ipsilesional PMd activation volume	−0.23	0.22	−0.04	0.82
Contralesional M1 activation volume	0.16	0.42	0.10	0.54
Contralesional PMd activation volume	−0.02	0.93	0.07	0.68
Activation laterality in M1	−0.18	0.39	−0.28	0.13
Activation laterality in PMd	−0.30	0.19	−0.25	0.20

M1 Primary motor cortex, *PMd* dorsal premotor cortex, *FA* fractional anisotropy

Correlation between independent variable and outcome measure ([a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$)

status, lower CST integrity (Fig. 1a), and absence of MEP (Fig. 1b). In 2 of the 6 categories (genetic and cortical function), no independent variable showed a significant bivariate relationship with impairment (FM score); the latter remained true when fMRI analyses were repeated excluding patients with direct stroke-related injury to M1 or PMd.

The 4 independent variables identified in bivariate screening were advanced into a multivariate model, where 2 of these (MEP absent and lower CST integrity by DTI) survived as significant predictors of greater impairment in the final model ($r^2 = 0.71$, $p < 0.0001$). Note that these 2 independent variables were not correlated ($p > 0.1$).

Correlates of impairment among patients with mild deficits

Analyses were repeated examining only the 9 patients in the top quartile of FM scores (FM score > 47). In bivariate screening, only one category had an independent variable significantly related to FM score, cortical function, where 3 instances were present: greater impairment was associated with a higher beta estimate in contralesional M1 ($p = 0.017$), higher beta estimate in contralesional PMd ($p = 0.02$), and greater lateralization of PMd activation toward the contralesional hemisphere ($p = 0.0496$). Because all significant independent variables in bivariate analyses were from the same category, multivariate modeling was not pursued.

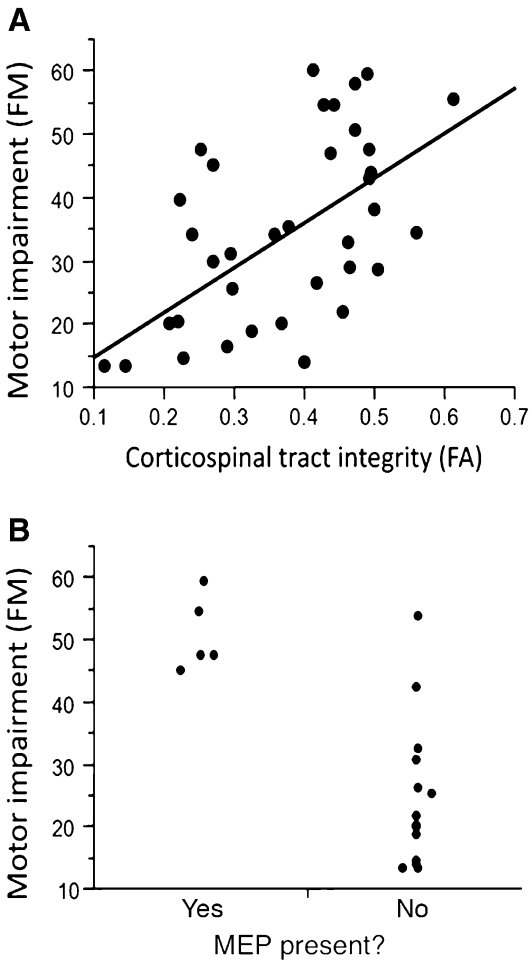

Fig. 1 Across all patients, the strongest bivariate relationships found with greater impairment (lower FM score) were **a** a measure of injury, lower CST integrity by FA ($r = 0.60$, $p = 0.0001$); and **b** a measure of neurophysiology, presence of MEP ($r = 0.74$, $p = 0.003$). These two measures remained significant in multivariate modeling

Correlates of disability (activities limitations)

When the 6 categories of independent variables were examined in relation to disability (mRS score), rather than impairment, a different pattern of findings emerged (Table 3). Bivariate screening identified independent variables significantly associated with mRS score in three categories: demographics/medical history (one instance), cognitive/mood (one instance), and brain injury (three instances). Specifically, greater disability (higher mRS score) was associated with presence of diabetes mellitus, poorer cognitive status (lower MMSE score), larger infarct volume, presence of M1 injury, larger cortical injury, and lower CST integrity by DTI.

The most significant independent variable from each of the 3 categories identified in bivariate screening was advanced into a multivariate model. Two of these, poorer cognitive status and lower CST integrity, survived as significant predictors of greater disability in the final model ($r^2 = 0.42$, $p = 0.0001$). Note that these 2 independent variables were not correlated ($p > 0.1$).

Discussion

Stroke is a very heterogeneous disease, and so not surprisingly numerous measures have been found to be associated with behavioral outcome. The current study used a multimodal approach to determine which measures are most strongly related to outcome by examining 6 categories in parallel. Greater impairment was most strongly related to measures of injury (lower CST integrity) and neurophysiological status (absent MEP), a pattern overall consistent with preclinical studies. Results differed when examining only patients with mild deficits, where measures of cortical function were most important, or when examining correlates of disability, where poorer cognitive status emerged as important. The correlates of outcome after stroke vary according to the patient subgroup or behavioral endpoint studied, a finding that may be important to many aspects of clinical trial design such as choice of entry criteria, stratifying variable, or biomarker.

Motor impairment was most strongly related to injury and neurophysiology. The injury measure, CST integrity using the DTI-based measure FA, reflects reduction in the directionality of water diffusion after stroke [34]. The correlation between lower CST integrity (lower FA) and poorer motor outcome (lower FM score) is consistent with prior studies [9, 35]. The neurophysiology measure, loss of MEP, reflects reduced function across motor cortex, CST, and motor unit [36]. The correlation between absent MEP and poorer motor outcome after stroke has also been reported [37]. The finding that CST integrity and neurophysiological status are the two factors mostly strongly related to motor impairment after stroke is in direct agreement with a study by Stinear et al. [38] that examined 4 of the 6 current measurement categories in 21 patients with chronic stroke. Measures of brain injury and of neurophysiology provide complementary insights after stroke: CST integrity by DTI was not correlated with neurophysiological status in the current cohort or in other populations [39, 40]; both measures remained significant in the multivariate model; and the multivariate model explained substantially more variance in motor impairment ($r^2 = 0.72$) than did either measure alone (DTI: $r^2 = 0.31$; neurophysiology: $r^2 = 0.55$). The current results are concordant with findings in the preclinical literature [12, 13], which emphasize that behavioral outcome after stroke is related to both extent of stroke injury and degree of residual function.

In this study, 2 variables that have previously been correlated with motor impairment did not exhibit such a relationship. First, infarct volume did not correlate with motor impairment, as has been described in prior studies [41, 42], possibly due to differences in study populations or procedures, and moreover did correlate with disability. A global measure of injury such as infarct volume does not provide any information about the lesion location and so might not be expected to provide precise insight into the functional state of any one neural system such as the motor system, but would be expected to correlate with global outcome measures. On the other hand, a motor system-specific injury measure such as CST integrity does provide specific insights into injury location and would be expected to correlate with motor status (FM score), as per Fig. 1a as well as previously published reports [29, 30, 43]. Together, the current constellation of findings support the idea that a global measure of injury (infarct volume) correlates more strongly with a global outcome measure (mRS score), while a neural system-specific measure of injury (CST integrity) correlates more strongly with an outcome measure specific to that system (arm motor FM score) [44]. Second, patients' depression scores also did not correlate with motor impairment. Prior studies have shown that post-stroke depression negatively impacts outcome [45, 46]. However, the primary reason depression was not related to motor impairment is likely because the patient sample herein was not, on average, depressed (median GDS = 2.5, normal = 0). Also, the demands placed upon a patient to enroll and then participate in the study may have introduced an ascertainment bias against subjects suffering from depression.

The current results emphasize that the measures most related to behavioral outcome after stroke vary across patient subgroups. When analyzing only those patients with mild deficits, greater impairment correlated with measures of cortical function (larger contralesional activation), in contrast with results when analyzing all patients, where impairment was related to injury and neurophysiology rather than cortical function. Given that greater motor impairment after stroke has a well-established relationship with increased activation in contralesional motor areas [10, 47], why in the current study did this relationship only emerge in the subgroup with mild motor impairment? The answer may rest with the fact that many previous studies have preferentially enrolled populations at the mild end of the impairment spectrum [14] or with small infarcts [48, 49]. This divergence of findings across patient subgroups suggests that restorative stroke trials might benefit from use of sliding outcomes [18], whereby the definition of treatment success differs across patient subgroups. Furthermore, the current results suggest that in restorative stroke trials, a singular approach to choosing stratification variables [50] or biomarkers [2] may be unwise.

The factors most strongly related to outcome also varied across WHO ICF dimensions. Using disability as the dependent measure rather than impairment resulted in a different constellation of findings: greater disability was associated with poorer cognitive status and reduced CST integrity. The association between greater disability and poorer cognitive status by MMSE is consistent with prior studies [51]. The current findings extend this observation and support recent models suggesting that functional status after stroke results from an interaction between cognitive status and motor system injury [52]. Multivariate modeling explained much less variance in disability ($r^2 = 0.42$) than in impairment ($r^2 = 0.71$), emphasizing that numerous complex factors influence disability after stroke. Finally, the incomplete correspondence between variables in the disability model and the impairment model is consistent with the fact that there is not a 1:1 relationship across WHO ICF dimensions [15].

Several limitations exist with the current study. The central results reflect correlation rather than causation, and the potential impact of mediating variables is difficult to estimate. Limited statistical power might have affected some analyses such as genetics, where very large samples sizes are customarily used to clearly identify relationships.

The BDNF val66met polymorphism and the ApoE4 allele have each been shown to correlate with stroke recovery [7, 53, 54], and each is also linked to important plasticity-related processes [55–57]. A cross-sectional study, such as the current one, measures final outcome whereas a longitudinal study captures the actual extent of recovery and so might better elucidate behavioral relationships with these plasticity-related genotypes. It is also noted that safety precautions precluded data collection in some patients, leading to a small subset of patients with neurophysiology data.

Conclusions

The current findings indicate that tissue injury and residual function are each related to motor outcome after stroke. Importantly, these relationships vary when examining different patient subgroups or when using an outcome measure from a different WHO ICF dimension. These findings may be instructive for the design of restorative stroke trials. Results also support the value of a multimodal approach for understanding outcomes after stroke [58]. Finally, the current findings support a body of data [50] suggesting that a measure of injury to a specific neural system (e.g., CST integrity) might be useful for distinguishing patient subgroups on a biological basis.

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